IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHIESI USA, INC., CORNERSTONE BIOPHARMA, INC., and EKR THERAPEUTICS, LLC, Plaintiffs, v. EXELA PHARMA SCIENCES LLC, EXELA PHARMSCI, INC., and EXELA HOLDINGS, INC., Defendants.	Civil Action No. 1:13-cv-01275-GMS [redacted]

PLAINTIFFS' ANSWERING CLAIM CONSTRUCTION BRIEF

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ABBREVIATIONS

Chiesi	refers to Plaintiffs Chiesi USA, Inc., Cornerstone BioPharma, Inc., and EKR Therapeutics, LLC
Exela	refers to Defendants Exela Pharma Sciences LLC, Exela PharmSci, Inc., and Exela Holdings, Inc.
Ex. __	refers to Exhibits to the *Declaration of Angus Chen, Esq.* dated February 20, 2015 (D.I. 54, Exs. 1–8) or Exhibits to the *Declaration of Angus Chen, Esq.* dated March 20, 2015 filed herewith (Exs. 9–12)
JA Ex. __	refers to Exhibits in the Joint Appendix of Intrinsic Evidence
Klibanov ¶ __	refers to the paragraphs in the opening declaration of Dr. Klibanov (D.I. 53, ¶¶ 1–63) or answering declaration of Dr. Klibanov filed herewith (¶¶ 64–119)

I. INTRODUCTION

Chiesi's claim constructions adhere to well-established claim construction principles and are consistent with the claims, specifications, and prosecution histories of the patents. They "stay[] true to the claim language and most naturally align[] with the patent's description of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005). In particular, Chiesi's construction of the "pre-mixed" term is based on the patentees' affirmative characterizations and unambiguous disclaimers, while Chiesi's construction of the "buffer" terms afford the full scope to which it is entitled in view of the absence of any disavowals. And Chiesi's expert (Alexander M. Klibanov, Ph.D.) has analyzed the evidence and confirmed that Chiesi's constructions are consistent with the understanding of a person of ordinary skill in the art ("POSA").[1]

In contrast, Exela's litigation-driven constructions selectively ignore intrinsic and extrinsic evidence, and add/import limitations that contradict the express teachings of the patents.[2] Exela's construction of the "pre-mixed" term improperly encompasses a diluted point-of-care[3] dosage form despite the patentees' clear and unmistakable disavowal thereof. And Exela's constructions of the "buffer" terms improperly add limitations absent from the specification ("separate and distinct") and import limitations from specific embodiments ("throughout the shelf-life of the product"), contradicting the specifications and a POSA's understanding of the claimed pharmaceutical compositions.

Chiesi respectfully requests that the Court adopt its claim constructions in their entirety.

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[1] The Supreme Court recently held that the review of extrinsic evidence, such as expert opinions regarding a POSA's understanding of the claim terms, is a factual finding subject to "clear error review." *Teva Pharm. USA, Inc. v. Sandoz, Inc*., 135 S. Ct. 831, 836-9 (2015).

[2] Exela failed to provide the level of skill of a POSA. (D.I. 56). The Federal Circuit has criticized constructions that "provide[] no analysis of the level of ordinary skill in this art . . ." *Nazomi Commc'ns, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1370–71 (Fed. Cir. 2005).

[3] *See* Chiesi's Opening Brief describing "point-of-care" versus pre-mixed/ready-to-use dosage forms. (D.I. 52 at 2-3).

II. EXELA'S "PRE-MIXED" CONSTRUCTION IGNORES THE UNAMBIGUOUS DISCLAIMERS OF BOTH THE CONCENTRATED POINT-OF-CARE DOSAGE FORM AND DILUTED FORM THEREOF

Claim Term	Chiesi's Proposed Construction	Exela's Proposed Construction
a pre-mixed aqueous solution	a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors	an aqueous solution that does not require reconstitution or dilution before administration to a patient.

Exela's construction of the term "a pre-mixed aqueous solution" is a litigation-driven attempt to overly broaden the claims and encompass a diluted concentrate dosage form. The prior art point-of-care product existed in two different forms: (i) a concentrated solution; and (ii) a diluted concentrate.[4] (Klibanov ¶¶ 70-71). Exela's Opening Brief recognized that the patentees distinguished the concentrated solution. (D.I. 56 at 5, 8-9). But Exela's brief failed to acknowledge that the patentees unambiguously disavowed the diluted concentrate form as well.

Exela's construction is overly broad as it encompasses the diluted concentrate form. This is evidenced by Exela's assertion that Chiesi's construction is "unduly narrow" by including the phrase "[already mixed] from the point of manufacture."[5] (D.I. 56 at 9). In other words, Exela's construction is broad enough to cover a dosage form that is mixed ***after*** the point of manufacture (i.e., the diluted concentrate form), which conflicts with the prosecution history of the patents

[4] The diluted concentrate point-of-care product is diluted ***after*** the point of manufacture but before administration (e.g., by a pharmacist who takes a concentrated product, dilutes the concentrate, and then supplies the diluted concentrate—which, at that point, does not require further dilution—to a medical care provider). (D.I. 52 at 2, 12; Klibanov ¶¶ 34, 70).

[5] Exela asserts that this phrase describes "an alternative embodiment not at issue in this case." (D.I. 56 at 9). But there was ***no disavowal*** of this aspect ***nor does Exela assert that there was one*** and, thus, the "pre-mixed" term should be entitled to its full scope (subject to disclaimers, *infra*). *Home Diagnostics, Inc. v. LifeScan, Inc*., 381 F.3d 1352, 1357 (Fed. Cir. 2004). Moreover, for the "buffer" terms, Exela itself relies on "alternative aspect[s]." (D.I. 56 at 12).

and ignores the disavowals by the patentees of ***both*** the concentrated point-of-care dosage form ***and diluted form*** thereof. Exela's construction should be rejected as a matter of law.

A patentee may limit the meaning of a claim term by making a "clear and unmistakable disclaimer." *Omega Eng'g, Inc, v. Raytek Corp*., 334 F.3d 1314, 1325-26 (Fed. Cir. 2003). Such a disclaimer may occur when the patentee distinguishes his invention over the prior art, such as by disparaging and criticizing its disadvantages. *Microsoft Corp. v. Multi–Tech Sys., Inc*., 357 F.3d 1340, 1349 (Fed. Cir. 2004); *Pacing Techs., LLC v. Garmin Int'l, Inc*., No. 2014-1396, 2015 U.S. App. LEXIS 2393, 7-8 (Fed. Cir. Feb. 18, 2015) ("We [] have found disclaimer when the patent repeatedly disparaged an embodiment . . . and then detailed the 'deficiencies [that] make it difficult' to use."); *Chi. Bd. Options Exch., Inc. v. Int'l Sec. Exch., LLC*, 677 F.3d 1361, 1372 (Fed. Cir. 2012) ("[The specification's] repeated derogatory statements about the [prior art] reasonably may be viewed as a disavowal of that subject matter from the scope of the Patent's claims."); *Astrazeneca AB v. Mut. Pharm. Co*., 384 F.3d 1333, 1340 (Fed. Cir. 2004).

The patentees made clear and unmistakable disclaimers here by distinguishing their invention from the prior art and its disadvantages. They "informed [] readers specifically why" ***both*** the concentrated form ***and diluted form*** thereof are ***not*** the claimed "pre-mixed" inventions. *Honeywell Int'l, Inc. v. ITT Indus*., 452 F.3d 1312 at 1319-20 (Fed. Cir. 2006).

Exela cannot deny that the patentees made clear and unmistakable disclaimers of both the concentrated point-of-care dosage form and the diluted concentrate form by distinguishing the claimed "pre-mixed" compositions from and disparaging the diluted concentrate forms. *First*, the patentees ***distinguished*** "the ***premixed*** formulation [] ***as an improvement over previous diluted samples of the prior art concentrate***" during prosecution. (JA Ex. F at A-134 (emphasis added)). *Second*, the patentees ***disparaged and criticized disadvantages*** of the diluted

concentrate form, stating that "[o]ne disadvantage is that the diluted solution is only stable for 24 hours at room temperature"; "[t]he diluted form must be discarded in 24 hours due to stability issues"; "[t]he selection of an inappropriate diluent can have an adverse effect on the stability and could cause breakdown of the drug"; and the "dilut[ed]" form has disadvantages with "contamination" problems. (JA Ex. A, '102 pat, col.1 ll.40-42; *see also* '102 pat, Ex. 1, Fig. 1, col.2 ll.41-44 (showing the instability of the diluted form); JA Ex. G at A-143 (emphasis added)). *Third*, the patentees ***distinguished*** the pre-mixed inventions because they "***overcome these disadvantages***" by providing "solutions for" and "address[] the[se] issues." (JA Ex. G at A-143; *see also* JA Ex. A, '102 pat, col.1 ll.51-57, col.2 ll.4-9 (emphasis added)). Thus, a POSA would understand that the patentees unambiguously disclaimed both the concentrate and the diluted concentrate from the claimed "pre-mixed" compositions.[6] (Klibanov ¶¶ 70-80).

Exela's attempt to include point-of-care dosage forms that are diluted after manufacture but before administration ignores the patentees' unambiguous disclaimers. Exela urges an overly broad construction that would improperly capture—rather than properly exclude—the disclaimed subject matter in order to fabricate an alleged invalidity defense. But "[t]he prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution." *Southwall Techs., Inc. v. Cardinal IG Co*., 54 F.3d 1570, 1576 (Fed. Cir. 1995). Further, as explained in Chiesi's Opening Brief, Exela's construction ***renders superfluous***, without any basis, a phrase that is already recited in certain independent claims ("wherein the aqueous solution requires no dilution before administration"). *See* D.I. 52 at 13; Klibanov ¶¶ 36, 81. Exela's construction should be rejected.

[redacted]

Chiesi's construction should be adopted in its entirety. Exela wrongly alleges that Chiesi's construction "read[s] in limitations." (D.I. 56 at 9). On the contrary, Chiesi's construction is supported by the intrinsic evidence, as well as the plain and ordinary meaning. (Klibanov ¶¶ 35, 72-80; Ex. 1, Bates at 151-152 (defining "Premixed" as "Manufacturer Prepared")). Chiesi defines the "pre-mixed" term with its advantages and in view of the patentees' disclaimers. (*See* D.I. 52 at 5-7.) At a minimum, the construction of "a pre-mixed aqueous solution" should exclude ***both*** the concentrated point-of-care dosage form ***and the diluted form*** thereof. *See* Ex. 3, *Markman* Order at 2-5, *Salix Pharms., Inc. v. Lupin Ltd.,* No. 12-1104 (D. Del. Dec. 17, 2013) (citing *Omega Eng'g., Inc*., 334 F.3d at 1325).

III. EXELA DID NOT CONSTRUE THE "ROOM TEMPERATURE" TERMS

Claim Terms	Chiesi's Proposed Construction	Exela's Proposed Construction
one year or three months "at room temperature"	one year or three months "full-term at room temperature"	No construction necessary.

Exela failed to construe the disputed "room temperature" terms in its Opening Brief, stating instead that it will address these terms for the first time in its Answering Brief. (D.I. 56 at 1 n.1). Any attempt by Exela to introduce affirmative argument regarding the "room temperature" terms in its Answering Brief is improper, untimely, and prejudicial to Chiesi. *Nuvasive, Inc. v. Globus Med., Inc.,* No. 10-849, 2013 U.S. Dist. LEXIS 97511, *9 (D. Del. July 12, 2013) (failing to provide a proposed construction "was entirely unhelpful to the Court and prejudicial to Globus, which only first had an opportunity to consider NuVasive's arguments against Globus' proposed constructions after reviewing NuVasive's answering brief"); s*ee also O2 Micro Int'l. Ltd. v. Beyond Innovation Tech. Co., Ltd*., 521 F.3d 1351, 1361 (Fed. Cir. 2008).

In any event, the Court should adopt Chiesi's constructions of the "room temperature" terms because they are supported by the intrinsic and extrinsic evidence. (D.I. 52 at 14-16; Klibanov ¶¶ 82-90). To the extent Exela asserts that the "room temperature" terms should include accelerated conditions (e.g., elevated temperatures for a period less than full-term), a POSA would understand from the disclosures in the specifications, FDA Guidances, [redacted] (Klibanov ¶¶ 86-89). Nowhere do the patents define these terms to mean accelerated conditions. (Klibanov ¶ 85). In fact, the specifications distinguish "accelerated conditions" from one year or three months "at room temperature." (*Id.*). Further, a POSA would understand that studies conducted under "accelerated" conditions are used merely to hypothesize the stability of a drug and that such hypotheses need to be verified with data from full-term room temperature studies. (Klibanov ¶¶ 85-89).

IV. EXELA'S ADDITION AND IMPORTATION OF LIMITATIONS INTO THE "BUFFER" TERMS SHOULD BE REJECTED BECAUSE IT CONTRADICTS THE INTRINSIC EVIDENCE

Claim Terms	Chiesi's Proposed Constructions	Exela's Proposed Constructions
buffer[7]	a system capable of maintaining the pH within an optimal pH range	Component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain an optimal pH range throughout the shelf-life of the product.

Exela's constructions for the "buffer" terms improperly add/import two limitations in order to create a purported noninfringement defense. Specifically, Exela's constructions require that a buffer (i) be "separate and distinct" from the other components of the formulations and (ii) maintain pH "throughout the shelf-life of the product." Exela adds a new "separate and distinct"

[7] *See* D.I. 52 at 16 for the parties' constructions of the related disputed term "buffer in an amount to maintain pH from about 3.6 to about 4.7."

limitation despite the fact that ***nowhere*** do the patents state that a "buffer" ***must*** be "separate and distinct" from other components. *See* D.I. 52 at 18. And Exela imports the "throughout the shelf-life of the product" limitation ***despite Exela's recognition*** that "Courts should ***not*** import limitations from the specification into otherwise unambiguous claim terms." (D.I. 56 at 7) (emphasis added). For these reasons, Exela's constructions should be rejected.

[redacted] Exela's new litigation-driven constructions should be rejected.

Exela fails to recognize the patents' teachings that one component may act as another component in the compositions. In particular, the specifications explicitly teach that acids, including citric acid, may be ***both*** a buffer ***and*** a pH adjuster. (*See* D.I. 52 at 18; Klibanov ¶¶ 46, 52-61, 100, 103-104). Moreover, Exela mischaracterizes other portions of the specifications. Ignoring the fact that the portions of the specifications upon which it relies only concern "***some*** embodiments," Exela ***erroneously*** states that "***every*** embodiment" disclosed in the patents lists a buffer as a separately-added component. (D.I. 56 at 12 (emphasis added); Klibanov ¶ 105). And the portions of the specifications that Exela cites do ***not*** prohibit a buffer from also serving as another component in the formulations. (Klibanov ¶¶ 105-108, 110-111). For example, Exela references Table 1 of the specifications to allegedly show embodiments where a citric acid buffer is a "separate and distinct" component. (D.I. 56 at 13). But, contrary to Exela's assertion,

nothing in Table 1 prevents citric acid from performing more than one function and the specifications state that citric acid can be both a buffer and a pH adjuster. (Klibanov ¶ 107).

Exela's reliance on the '405 patent cited during prosecution that relates to a point-of-care nicardipine dosage form—a product distinct from the claimed inventions at issue in this litigation—is similarly misplaced. Specifically, Exela cites the formulation of Example B of the '405 patent to argue that "buffer, namely citric acid monohydrate and sodium hydroxide" was added to the formulations to maintain the pH. (D.I. 56 at 16). ***But Exela ignores the fact that the '405 patent teaches that both citric acid and sodium hydroxide can also perform the function of a pH adjuster.*** (JA Ex. K, '405 patent, col.5, ll.5-9; Klibanov ¶¶ 113-115). Thus, based on the express teachings of the '405 patent, a POSA would understand that citric acid and sodium hydroxide can be both a buffer and a pH adjuster. (Klibanov ¶¶ 112-116).

Exela's argument that the structure of the independent claims requires that a buffer be "separate and distinct" is wrong. (D.I. 56 at 10-11). There is "no reason why, as a matter of law, one claim limitation may not be responsive to another merely because they are located in the same physical structure." *Intellectual Prop. Dev., Inc. v. UA-Columbia Cablevision of Westchester, Inc*., 336 F.3d 1308, 1320 n.9 (Fed. Cir. 2003). The Federal Circuit has instructed that whether recited claim elements must be separate and distinct is a fact-specific inquiry. For example, in *Linear Tech. Corp. v. I.T.C.*, the Federal Circuit rejected the argument that the claim terms "second circuit" and "third circuit" must be "entirely separate and distinct," stating that "the 'second' and 'third' circuits must only perform their stated functions" and "can contain overlapping components." 566 F.3d 1049, 1055-56 (Fed. Cir. 2009). Absent a clear disavowal

or a contrary definition, a patentee is entitled to the full scope of a claim term. *Id*. at 1055 (*citing Home Diagnostics*, 381 F.3d at 1357). There is no such disavowal or contrary definition here.[8]

Exela's reliance on *Becton, Dickinson & Co. v. Tyco Healthcare Group*, 616 F.3d 1249 (Fed. Cir. 2010), is misplaced. In *Becton*, the Federal Circuit held that whether a patent claim separately lists components alone does not determine whether they must be separate and distinct; ***there must also be an "absence of any evidence to the contrary."*** *Id.* at 1254 (citation omitted) (emphasis added). The patent specification in *Becton* indicated that two components, a springed means and a hinged arm, must be separate and distinct because if they were the same, the claims would be "nonsensical" and a "physical impossibility." *Id.* at 1255. And "if the hinged arm and spring means [were] not separate structures, then the asserted claims [were] clearly invalid as obvious over the prior art." *Id.* Thus, the court relied on the specific teachings of the specification and preserved claim validity. *See also Powell v. Home Depot U.S.A., Inc.,* 663 F.3d 1221, 1231-32 (Fed. Cir. 2011) (distinguishing *Becton* as involving (i) claims that did not suggest two elements could be the same structure, and (ii) a specification that "confirmed" the two elements were separate). There is no "nonsensical" result or "physical impossibility" here.

Nothing in the patents precludes one component from also acting as another component. In fact, the specifications explicitly teach that a component may serve more than one purpose. (Klibanov ¶¶ 53, 93-94, 103-105; D.I. 52 at 18). Exela selectively ***ignores*** this and ***fails*** to point

[8] Exela focuses on certain claims, such as claim 11 of the '290 patent, as "recit[ing] separately adding 'citric acid' to the compositions to form a separate citrate buffer." (D.I. 56 at 11). But Exela mischaracterizes these claims—neither claim 11 nor any other claim of the patents state that the citric acid is added solely as a buffer to the exclusion of other functions. (*See, e.g.,* JA Ex. B, '290 patent, claim 11; Klibanov ¶¶ 99-102). A POSA would understand that the citric acid recited in certain claims is not limited to only being a buffer, but can also perform other functions, such as a pH adjuster. (Klibanov ¶¶ 97-111).

to any requirement that a buffer ***must*** be separate and distinct from other components.[9] (Klibanov ¶¶ 103-111). Moreover, Exela provides no evidence that Chiesi's constructions would render the claims nonsensical or physically impossible. *Contra Becton*, 616 F.3d at 1255.

Second, Exela's Opening Brief is tellingly silent regarding Exela's improper importation of the phrase "throughout the shelf-life of the product." (D.I. 56). Notably, this phrase refers only to "***some*** embodiments." (*See* D.I. 56 at 12 (citing JA Ex. A, '102 pat., col.4 ll.20-31 (emphasis added); Klibanov ¶¶ 62, 95, 119). As explained in Chiesi's Opening Brief, the specifications teach other embodiments that expressly do ***not*** require pH to be maintained throughout the shelf-life (which Exela ignores). (D.I. 52 at 19-20; Klibanov ¶¶ 62, 119). Thus, a POSA would understand that there is no requirement that the inventions are limited to a buffer that maintains pH "throughout the shelf-life of the product." (Klibanov ¶¶ 62-3, 95, 119).

Exela's constructions should be rejected.[10] They improperly add/import limitations into the claims that are inconsistent with the patents, and a POSA's understanding.[11] (Klibanov ¶¶ 88-93). In doing so, Exela commits "[o]ne of the cardinal sins of patent law." *Phillips*, 415 F.3d at 1319-20. Chiesi's constructions, on the other hand, recognize that the "buffer" terms are entitled to their full scope, and should be adopted. *Home Diagnostics*, 381 F.3d at 1357.

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[9] Exela's conclusory assertion that "[t]he *reason* a buffer is *separately* added" is to maintain the pH of the compositions to ensure stability throughout the shelf-life is devoid of any support. (D.I. 56 at 13 (emphasis added); Klibanov ¶ 109).

[10] This is not the first time that Exela has attempted to import limitations into a "buffer"-related term in this District. *Cadence Pharms. Inc., v. Paddock Labs., Inc.,* 886 F. Supp. 2d 445, 456 (D. Del. 2012). As in *Cadence*, Exela's "buffer" construction should be rejected.

[11] Exela's brief is also silent regarding its attempt to import a ***single*** "[c]omponent" as a limitation. (D.I. 52 at 19 n.10). A POSA would understand—and the specifications explicitly state—that a "buffer" in the context of the patents may be ***one or more*** components of the claimed formulations that maintain pH within the optimal pH range. (Klibanov ¶¶ 117-118).

V. CONCLUSION

Chiesi's constructions are consistent with both the intrinsic and extrinsic evidence. They account for the patentees' unambiguous disclaimers, and most naturally align with the patents. Exela's constructions conflict with both the intrinsic and extrinsic evidence; in particular, they ignore the patentees' disclaimers of the diluted point-of-care dosage form from the "pre-mixed" term, and improperly add and import limitations into the "buffer" terms that contradict the specifications. Accordingly, Chiesi's constructions should be adopted in their entirety.

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